

# Evidence for a Higher Risk of Hypovolemia-Induced Hemodynamic Instability in Females: Implications for Decision Support During Prehospital Triage

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**ABSTRACT** Lower body negative pressure (LBNP) simulates hemorrhage, and tolerance to LBNP (time to presyncope [TTP]) is indicative of tolerance to blood loss. The purpose of this study was to predict TTP based on demographic characteristics (sex, age, height, and body mass index) and physiological variables (heart rate [HR], systolic arterial pressure, diastolic arterial pressure [DAP], pulse pressure, stroke volume, total peripheral resistance [TPR], and baroreflex sensitivity [BRS]) at baseline, and during 2 levels of LBNP (−15, −30 mm Hg). Multiple linear regression analysis was used to create a model to predict TTP (range: 670 to 2516 seconds,  $n = 187$ ) based on demographic characteristics and physiological variables changes ( $\Delta$ ) from baseline to −30 mm Hg LBNP. The prediction model revealed that TTP (seconds) =  $1667.5 + (5.1 \times \text{Age}) + (61.1 \times \text{Sex}) - (21.5 \times \Delta\text{HR}) + (55.3 \times \Delta\text{DAP}) - (88.2 \times \Delta\text{TPR}) - (4.9 \times \Delta\text{BRS})$ . Most significantly, our analysis demonstrated a lesser survival trajectory for females given the same rate and magnitude of hemorrhage compared to males. Young age and female sex are predictors of low tolerance to blood loss, and should be considered for early triage in the prehospital setting.

## INTRODUCTION

A recent review by Eastridge et al<sup>1</sup> revealed that greater than 85% of deaths that occurred on the battlefield (before reaching a medical treatment facility) were predominantly because of hemorrhage and more importantly, 25% were classified as potentially survivable. These findings clearly identify the need to develop strategies to help improve care and triage procedures administered by combat medics. Although there are multiple factors that contribute to death from hemorrhage, one factor that should be considered is the patient's tolerance to hemorrhage which is defined by the failure of compensatory mechanisms to maintain adequate tissue perfusion, subsequently leading to cardiovascular collapse (circulatory shock) and death. Clinical studies<sup>2,3</sup> have shown that tolerance varies among patients such that for similar rates of blood loss, some individuals will reach the point of cardiovascular collapse in a shorter amount of time compared to other individuals. These low-tolerant individuals are subsequently at a higher risk of death during hemorrhage and would require early implementation of lifesaving maneuvers. Predicting a soldier's predisposition for hemorrhagic shock before injury could improve survivability in the event of a battlefield injury. Unfortunately, relative intolerance to hemorrhage is typically recognized during actual blood loss, when potentially effective intervention may be applied too late. A metric that predicts tolerance to blood loss could be used to identify those individuals who are

at high risk for the onset of overt hemorrhagic shock, and reduce killed in action of potentially survivable casualties.

Lower body negative pressure (LBNP) induces central hypovolemia similar to hemorrhage,<sup>4,5</sup> and thus provides a test bed for evaluating the factors that affect an individual's ability to compensate to blood loss. Tolerance to hypovolemia with LBNP is highly variable and repeatable among individual humans,<sup>6–9</sup> and approximately 35% of LBNP subjects exhibit a low tolerance to central hypovolemia.<sup>8,10</sup> Many studies have searched for predictors of tolerance, and the most consistent finding is that females have a lower tolerance to hypovolemia compared to males.<sup>6,11–16</sup> This finding is particularly relevant to improving survival from battlefield trauma since the number of women sustaining battlefield injuries is likely to increase as women are now eligible for infantry, artillery, and other battlefield assignments. In addition to being female, other physical characteristics, resting cardiovascular parameters, and hemodynamic responses to LBNP have also been identified to be related to tolerance.<sup>10,12,17–22</sup> Consequently, there are multiple variables that appear to contribute to tolerance, but their relative importance to predicting outcome is limited by the specific physiological measurements available to battlefield medics.

LBNP experiments conducted in our laboratory have resulted in a database of more than 200 male and female subjects ranging in age from 18 to 55 years with multiple cardiovascular measures obtained from simple and more complex noninvasive monitoring devices. Using this extensive database, we evaluated multiple demographic and physiological variables, which may account for the variability in tolerance to blood loss in any given individual. We tested the hypothesis that a mathematical model of easily attainable parameters could predict high probability for risk of developing circulatory shock using LBNP as model of hemorrhage.

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## METHODS

The protocol was approved by the Institutional Review Board of Brooke Army Medical Center, Fort Sam Houston, Texas. All studies were conducted at the U.S. Army Institute of Surgical Research, Fort Sam Houston, Texas. Normotensive, nonsmoking healthy human volunteers ( $N = 202$ ) participated in this study after evaluation of their medical history and physical examination by a physician to ensure the absence of previous and current medical conditions that would exempt them as participants. Body mass index (BMI) was calculated as the ratio of mass to height. Subjects were instrumented for standard lead II electrocardiogram to record heart rate (HR), and a finger photoplethsmography cuff (Finometer) to record beat-by-beat finger systolic and diastolic arterial pressure (SAP, DAP). Pulse pressure (PP) was calculated as the difference between SAP and DAP. Stroke volume (SV) was derived from the arterial pressure waveform from the finger photoplethsmography cuff, and used to calculate total peripheral resistance (TPR). Cardiac baroreflex sensitivity (BRS; a reflex increase in HR initiated by a reduction in blood pressure) was determined from spontaneous fluctuations in R-R interval and DAP using WinDAQ data acquisition software (Dataq Instruments, Akron, Ohio) and WinCPRS data analysis software (Absolute Aliens, Turku, Finland).

Reduction in central circulating blood volume similar to that observed in hemorrhage was induced by application of LBNP. Subjects were positioned supine within an airtight chamber that was sealed at the level of the iliac crest by a neoprene skirt. The LBNP protocol consisted of a 5-minute control period (baseline) followed by 5 minutes of chamber decompression at  $-15$ ,  $-30$ ,  $-45$ , and  $-60$  mm Hg, and then additional increments of  $-10$  mm Hg every 5 minutes until the onset of cardiovascular collapse (presyncope) followed by a 10 minute recovery period. Cardiovascular collapse was identified in real time by the attending investigator by a precipitous fall in SAP greater than 15 mm Hg concurrent with the onset of presyncopal symptoms such as bradycardia, grayout (loss of color vision), tunnel vision, sweating, nausea, or dizziness. Based on these criteria, 187 of 202 subjects attained presyncope. Time to presyncope (TTP) was calculated from the start of baseline to termination of LBNP.

Data are presented as mean  $\pm$  SD. Sex differences in physical characteristics were determined by  $t$  test. Kaplan-Meier survival curves were used to evaluate TTP in all subjects. Survival curves between males and females were compared using the log-rank test.

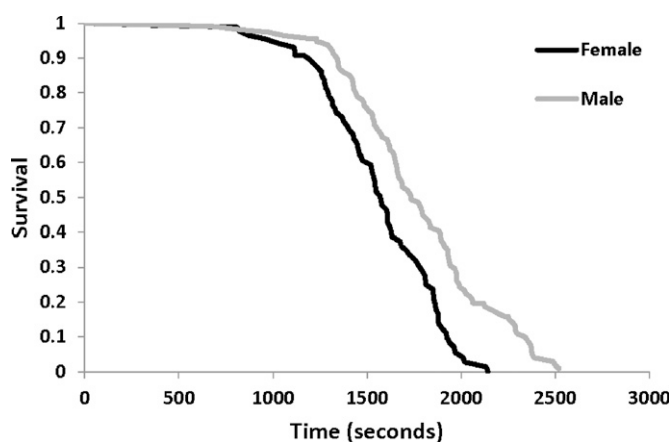
The variance in TTP conferred by demographic data (sex, age, height, and BMI) and physiological variables (HR, SAP, DAP, PP, SV, TPR, and BRS) was systematically evaluated at baseline, and during the first two levels of LBNP ( $-15$  and  $-30$  mm Hg). Multiple linear regression analysis determined the contribution of demographic and physiological variables to the variance in TTP in presyncopal subjects ( $n = 187$ ). Factors with the largest  $p$  values were removed by backwards

elimination until only factors with a  $p$  value less than 0.20 remained in the equation.

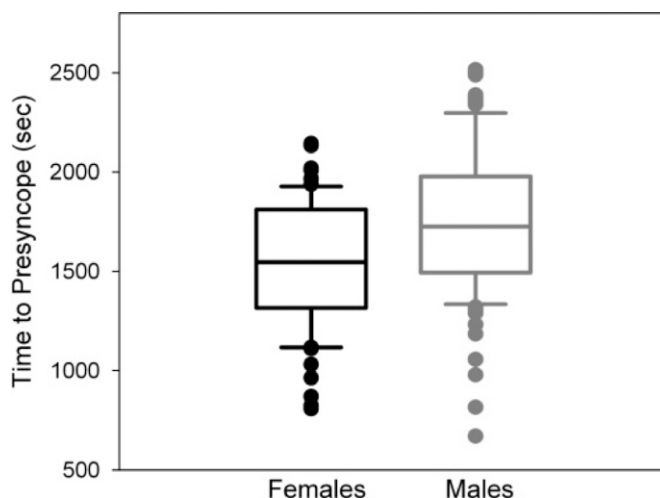
## RESULTS

### Demographic Characteristics

From the study population of 202 subjects, male subjects ( $n = 115$ ) were older ( $29 \pm 8$  years versus  $27 \pm 8$ ,  $p = 0.044$ ), taller ( $179 \pm 8$  cm versus  $165 \pm 7$  cm,  $p < 0.0001$ ), and had a greater BMI ( $26.2 \pm 3.9$  versus  $23.2 \pm 2.9$ ,  $p < 0.0001$ ) than female subjects ( $n = 87$ ). Kaplan-Meier survival curves included 15 censored subjects (did not attain presyncope), and log-rank test revealed that TTP was greater ( $p < 0.001$ ) in males than females (Fig. 1). In the 187 presyncopal subjects, the range of TTP was 670 to 2516 seconds (Fig. 2). The average TTP in males ( $1756 \pm 370$  seconds,  $n = 109$ ) was greater than females ( $1546 \pm 307$  seconds,  $n = 78$ ). Despite



**FIGURE 1.** Kaplan-Meier survival curves in males (gray) and females (black). Log-rank test indicated difference between males and females,  $p < 0.0001$ .



**FIGURE 2.** Box (25th/75th percentiles) and Whisker (90th/10th percentiles) plots with median (solid line) values in presyncopal male (gray) and female (black) subjects. Mean time to presyncope values in males ( $1756 \pm 370$  seconds) and females ( $1546 \pm 307$  seconds) were different,  $p < 0.01$ .

these sex differences in TTP, regression analysis indicated that sex accounted for 8% of the variance in TTP ( $R^2=0.083$ ). The combination of all demographic factors (sex, age, height, and BMI) accounted for 9% of the variance in TTP.

### Physiological Variables

At baseline, resting levels of physiological variables in combination with physical factors explained the variance in TTP by 11%. This contribution to TTP variance was improved if changes in physiological variables were assessed during the first two steps of LBNP. The explained variance in TTP was 23% at  $-15$  mm Hg LBNP, and increased further to 37% at  $-30$  mm Hg LBNP. A final model of two demographic factors (age and sex), and changes in four physiological variables ( $\Delta$ HR,  $\Delta$ DAP,  $\Delta$ TPR, and  $\Delta$ BRS) in response to  $-30$  mm Hg LBNP maximized the predictive power that can be expressed in the following equation:

$$\begin{aligned} \text{TTP(seconds)} = & 1667.5 + (5.1 \times \text{Age}) + (61.1 \times \text{Sex}) \\ & - (21.5 \times \Delta\text{HR}) + (55.3 \times \Delta\text{DAP}) \\ & - (88.2 \times \Delta\text{TPR}) - (4.9 \times \Delta\text{BRS}) \end{aligned}$$

### DISCUSSION

Using LBNP to simulate hemorrhage, we investigated physiological responses to reduced circulating central blood volume in more than 200 healthy human volunteers with similar demographics as military personnel. This study evaluated four demographic characteristics and seven cardiovascular measurements at baseline and during the “early” stages of LBNP to identify metrics that can be used in a mathematical model for the determination of tolerance to hemorrhage before the early decompensatory phase of shock. There were three major findings from this study. First, the average LBNP tolerance time to cardiovascular collapse was less in females. Second, the inclusion of cardiovascular responses to  $-30$  mm Hg LBNP improved the prediction model. Third, multiple regression analyses revealed that the best prediction model included six factors: sex, age,  $\Delta$ HR,  $\Delta$ DAP,  $\Delta$ TPR, and  $\Delta$ BRS. These factors accounted for 11% of TTP variance at baseline, but improved to 37% of TTP variance when changes in these cardiovascular variables were assessed during  $-30$  mm Hg LBNP.

Although the sex differences in tolerance time to hemorrhage simulated by LBNP have been previously reported,<sup>6,11–16</sup> two studies have assessed the contribution of sex and physiological variables to predicting tolerance.<sup>18,23</sup> Using the same computational model as this study, but a smaller and younger population of 47 subjects, Franke et al<sup>18</sup> identified predictors of tolerance to LBNP as sex, resting TPR, and  $\Delta$ HR during  $-40$  mm Hg LBNP, and  $\Delta$ HR at presyncope. Most recently, Wallace et al<sup>23</sup> used a structural equation model in 125 sub-

jects to identify sex, percentage of body fat, resting TPR, and  $\Delta$ HR at presyncope as variables that influence LBNP tolerance. The results of this study support previous observations that sex, age, and early changes in HR are predictors of tolerance,<sup>18,19,23</sup> and extend our operational applications by providing new evidence that early changes in DAP, TPR, and BRS can also be used to predict an individual’s predisposition for developing hemorrhagic shock. Most important, our analysis demonstrates a lesser survival trajectory for females given the same rate and magnitude of hemorrhage compared to males (Fig. 1).

LBNP exposure elicits a baroreflex-mediated increase in HR and TPR to maintain DAP at a normal level during the progression of reduced central blood volume.<sup>24</sup> We have shown that low-tolerant individuals have a lesser capacity to increase HR and TPR during maximum LBNP exposure than high-tolerant individuals.<sup>7,20</sup> Similarly, progressive withdrawal of cardiac parasympathetic influence (i.e., reduced cardiac BRS coincident with central blood volume reduction) is blunted in low-tolerant individuals.<sup>21</sup> Although not all females have a low tolerance to blood loss, factors such as less-relative blood volume, and reduced SV, vasoconstrictor and HR responses to hypovolemia that contribute to low tolerance have been identified as more prominent in females compared to men.<sup>13,14,22,25–27</sup> The blunted vasoconstrictor response to LBNP in women has been shown to be the effect of estrogen to blunt baroreflex-mediated vasoconstrictor responses.<sup>22</sup> Therefore, it is not surprising that female sex and early changes in HR, TPR, DAP, and BRS proved to be significant predictive variables of tolerance in this study. Based on the mathematical model proposed in this study, young age and female sex proved to be predictors of low tolerance to hemorrhage. Early changes in HR, TPR, and BRS have an inverse relationship with tolerance which means that the larger the changes in these variables during  $-30$  mm Hg LBNP, the less tolerant a person will be. The early change in DAP is proportional to tolerance, therefore decreases in DAP in response to  $-30$  mm Hg is predictive of low tolerance.

To evaluate the relative importance of sex as a variable in a prediction model, the complexity of the model must be considered. The proposed 6-variable prediction model has 3 variables (early changes in HR, TPR, and BRS) that can be influenced by female sex.<sup>14,22,27</sup> The accuracy of complex prediction models that include multiple variables affected by sex is not usually improved by including sex as an independent variable. An excellent example of such a complex model is the decision support tool our group is developing known as the Compensatory Reserve Index that accurately indicates the hypovolemic status of the patient without inclusion of sex as an input variable.<sup>8,28</sup> However, if the model is simple with few factors that are not influenced by sex, then including sex as a variable would improve the accuracy of a decision support tool.

Treatment of combat-wounded soldiers on the battlefield and their transport to a medical treatment facility requires

quick and efficient responses from the combat medic and the prehospital medical team. First responders must be able to assess the severity of trauma, determine when lifesaving interventions are immediately required, and prepare patients for transport. Factors such as multiple casualties, hostile environments, and long evacuation routes often increase the time until a casualty receives advanced medical treatment. Since more than 90% of potentially survivable deaths on the battlefield were because of hemorrhage, accurate triage of bleeding patients could improve survivability of combat casualties. Unfortunately, the time to cardiovascular collapse in a bleeding patient is highly variable and difficult to predict. Therefore, in response to the need for methods to improve survivability on the battlefield, we propose that the results of this study can be used to train combat medics to recognize and respond to predictors of low tolerance to hemorrhage when triaging and treating wounded soldiers. The demographic characteristics of young age and female sex are the most easily assessed predictors of low tolerance, and consequently identify individuals for priority triage. If the medic can monitor vital signs, then the data of this study support the use of rapid increases in HR and decreases in blood pressure as strong predictors of low tolerance. For a more thorough assessment, we propose that the use of simple tests (e.g., stand or tilt test) that produce hemodynamic changes similar to or greater than the acute central hypovolemia induced by  $-30$  mm Hg LBNP may provide a simple test to determine tolerance to blood loss before deployment.<sup>29</sup> These tests could be used to identify those individuals that have a low tolerance to hypovolemia, and are at highest risk for cardiovascular collapse during hemorrhage. This information could be made available to the combat medic to provide more efficient treatment in the event of traumatic injury. Whether the medic is trained to recognize predictors of low tolerance to hemorrhage, or soldiers are tested for low tolerance before deployment, the ability to assess tolerance to hemorrhage in a wounded soldier could potentially lead to limiting the number of deaths that occur on the battlefield.

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